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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,036	12/10/2001	Michel Koehl	017753-150	8634

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,036	KOEHL ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,19-34 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-34 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 15, 2005 has been entered. Claims 19-34 and 36-38 are pending and under examination.

2. The objection to claim 38 is withdrawn in view of Applicant's amendment.

Claim Rejections - 35 USC § 103

3. The rejection of claims 19-38 as rejected under 35 U.S.C. 103(a) as unpatentable over Shabram *et al.* (WO 96/27677 A2, "Shabram") in view of Berg (WO 98/33572 A1), Bondoc *et al.* (*J. Indust. Micro. & Biotech.*, 1998, "Bondoc") and Blanche *et al.* (WO98/00524, English version is US Patent 6,458,958) is withdrawn because the limitation for which Blanche *et al.* was introduced has been deleted from the claims in the amendment filed march 15, 2005.

4. Claims 19-34 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shabram in view of Berg, Bondoc and Georgiou et al. (US 6,027,888, "Georgiou"). The claims amended are drawn to a method for purifying adenoviral particles from a crude viral preparation comprising fluidized bed chromatography and gel filtration chromatography. Specifically, the method involves contacting the preparation with particles of adsorbent in a fluidized bed, eluting

the adsorbed adenoviral particles from the adsorbent particles and collecting the eluted adenoviral particles. The particles of adsorbent are comprised of an agarose matrix and a central core comprising quartz (Streamline®XL type or Streamline®Q XL type). Dextran chains are covalently coupled to the matrix, and positively charged groups (Q groups) are attached to the matrix. The support for the gel filtration chromatography step comprises alkyl dextran and methylene bisacrylamide matrix, or ethylene glycol and methacrylate matrix. Further limitations of the claims have been addressed previously.

The teachings of Shabram are of record. To summarize, Shabram teaches a method of purifying recombinant adenoviruses (viral vectors for use in gene therapy) from a cell lysate comprising two chromatography steps (fluidized-bed adsorption followed by immobilized metal affinity column (IMAC) or hydrophobic interaction chromatography (HIB)), see abstract, page 4, lines 5-10, page 8, lines 4-8, and page 9, lines 13-15. Shabram uses a cross-linked agarose column (page 11, lines 27-28). The salt concentration of the eluant is diluted to about 450 millimolar or less in order to prevent premature stripping of viral particles from the exchange resin (page 12). A buffer is used to maintain the pH of the cell lysate solution between about 5.0 and 9.0. During chromatography, the resins are treated by flushing with NaCl and water. Shabram also discloses the production of adenoviral vectors from cell lines (page 15), lysis (page 17) and nucleic acid degradation (page 18). Shabram fails to teach the step of gel filtration and the specific type of adsorbent particle as instantly claimed.

Bondoc teaches a method of purifying recombinant adenovirus (rAd5) using size exclusion chromatography, also called gel filtration (page 318, first column, third full paragraph). Georgiou discloses that alkyl dextran can be cross-linked with methylene

bisacrylamide for gel filtration chromatography (col. 38, lines 44-65). It would have been obvious to use the materials described in Georgiou for Bondoc's gel filtration. One would have been motivated to use the materials because Bondoc's disclosure does not detail the specific materials to be used, and Georgiou provides a general description of the materials to be used in gel filtration. One would have had a reasonable expectation of success that the materials described by Georgiou would have worked in Bondoc's gel filtration because Georgiou also uses the materials for gel filtration chromatography, as in Bondoc.

Berg teaches a method for adsorption of a substance from a liquid sample on a fluidized bed, in which the total yields are improved. The beads used in the method comprise a structure/ligand linked to a base matrix (bead) via an extender. The base matrix is comprised of cross-linked agarose (page 8, lines 28-33) and a bead filler of quartz (page 9, lines 30-31). Dextran is covalently bound to the agarose matrix (page 5, lines 2-17).

It would have been obvious to modify Shabram's method by substituting Bondoc's step of gel filtration with Shabram's step of IMAC. One would have been motivated by Bondoc's teaching that gel filtration chromatography can be substituted for zinc metal-chelating chromatography, a form of IMAC (page 318, first column, third full paragraph). One would have had a reasonable expectation of success that the gel filtration step would have resulted in purified adenoviruses because Bondoc reports that the adenovirus particles obtained by gel filtration were comparable with those obtained with the standard cesium chloride (CsCl) gradient-method page 318, first column, third full paragraph). It would have been obvious to use the adsorbent particles taught by Berg in Shabram's method. One would have been motivated to use Berg's adsorbent particles because Berg's method is aimed at improving total yields and

productivity in adsorption processes on fluidized beds, and providing filler matrices that have improved breakthrough capacity in fluidized beds (page 4, lines 15-21). One would have had a reasonable expectation of success that the adsorbent particles of Berg would have improved Shabram's method because Berg's adsorbent particles are intended for use in methods of adsorption using fluidized beds.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that Shabram's disclosure regarding the use of fluidized bed chromatography is limited to an all-inclusive list which fails to render the claims obvious. Applicant also argues that Shabram teaches that the use of cross-linked agarose columns is in the same paragraph that discusses hydrophobic interaction chromatography. Therefore, there is no motivation to perform anion exchange chromatography in a fluidized bed using an agarose matrix and a central core.
    - In response, the fact that Shabram suggests the use of fluidized bed chromatography in one sentence in the whole document is not evidence that one of ordinary skill in the art would not have considered it to be an alternate method. Further, regarding the use of cross-linked agarose, Shabram teaches in general that the support material can be cross-linked dextran and cross-linked agarose (page 9, lines 1-12). Therefore, Shabram suggests the use of fluidized bed chromatography and the support comprising agarose/dextran.
- Applicant argues that Shabram fails to suggest the combination of the two claimed chromatographic steps (anion exchange chromatography in fluidized bed followed by gel

filtration chromatography). Applicant points to Huyghe's article (*Human Gene Therapy*, 6:1403, 1995) as evidence that recovery of virus off a gel filtration column was very low. In view of Shabram's lack of motivation to use both methods and Huyghe's experimental data showing that recovery of virus was low using gel filtration, there is no motivation to combine the two methods together.

- In response, the teachings of Huyghe do not directly relate to the claimed method. The claimed method requires the use of both methods (fluidized bed and gel filtration). The use of a single method is not expected to have the same result as the use of both methods. Applicant is arguing that the results with a single method would dissuade one of ordinary skill to not consider the use of the method. However, one of ordinary skill knows that other factors weigh into the choice of a method besides the results of one experiment. The motivation to combine the methods comes from Bondoc, which teaches that IMAC can be substituted with gel filtration chromatography (Bondoc, page 318, first column, third full paragraph).

- Applicant argues that Shabram's own research teaches against the presently claimed combination. Applicant argues that based on Shabram's results (15-20% recovery of virus) one would not be motivated to combine a poor yielding step with any other step.
    - In response, the Huyghe reference is not part of the rejection, rather Applicant is pointing to particular teachings in Huyghe. Applicant is basing arguments, not on the references used in the rejection, but references that are not in the rejection to provide support. If Applicant intends to rely on the teachings of Huyghe, the

arguments would best be presented in a declaration. Further, the claims do not recite percent production/recovery of viruses. Applicant removed that limitation in the most recent amendment.

- Applicant argues that Bondoc's teachings relating to purification of adenovirus is merely incidental and bare at best.
    - In response, the teachings of Bondoc, regardless of the degree of importance of adenovirus purification, are the teachings of Bondoc. Bondoc has disclosed information that one of ordinary skill in the art would have had available for use. Applicant's arguments are opinions only and do not address the facts.
- Berg does not suggest that viruses could be purified with the fluidized bed process. Berg teaches that fluidized bed chromatography is normally limited to compounds having a molecular weight below 1,000,000 daltons. One would not have had a reasonable expectation of success with purifying adenoviruses because the size of the adenovirus is about 150 fold above Berg's teaching that the normal weight is below 1,000,000 daltons.
    - In response, it is the Office's position that Berg is not excluding the use of fluidized bed chromatography for larger compounds. Note that Shabram discloses the use of a fluidized bed for purifying recombinant viral vectors (discussed above). Applicant has not provided evidence that fluidized bed chromatography for purifying viruses was discouraged. Berg only teaches the "usual" molecular weight and does not discourage purification of larger molecules.

Conclusion

5. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
July 27, 2005